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A Review: Development of New Anticancer Drugs Complementary to Transition Metal Complexes Such as Copper(II), Zinc(II), Nickel(II) and Cobalt(II)

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ABSTRACT

It has been established that the properties of Cu(II), Zn(II), Ni(II) and Co(II) coordinated compounds are largely determined by the nature of ligands and donor atoms bound to the metal ion. In this review, the most remarkable achievements in the design and development of copper(I, II) complexes as antitumor agents are discussed. Special emphasis has been focused on the identification of structure-activity relationships for the different classes of copper(I,II) complexes. This work was motivated by the observation that no comprehensive surveys of copper complexes as anticancer agents were available in the literature. Moreover, up to now, despite the enormous efforts in synthesizing different classes of copper complexes, very few data concerning the molecular basis of the mechanisms underlying their antitumor activity are available. This overview, collecting the most significant strategies adopted in the last ten years to design promising anticancer compounds, would be a help to the researchers working in this field.

Keywords: Anticancer drugs, Cu(II), Zn(II), Ni(II) and Co(II).

INTRODUCTION

Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated by ligands.

(Cox, 2005). Due to exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal based drugs with promising pharmacological application and may offer unique therapeutic opportunities. (Rafique *et al*., 2010). These complexes show a great diversity in action. (Hariprasath *et al*., 2010). Medicinal inorganic chemistry can exploit the unique properties of metal ions for the design of new drugs. This has, for instance, led to the clinical application of chemotherapeutic agents for cancer treatment, such as cisplatin. (Pieter *et al*., 2008) nickel(II) isothiocyanato complex. The use of transition metal complexes as therapeutic compounds has become more and more pronounced. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Beside all these limitations and side effects transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics in a way that is, unimaginable in few years back. (Rafique *et al*., 2010). Transition metal complexes are important in catalysis, materials synthesis, photochemistry, and biological systems. With a critical overview of the present advancement in these areas, this review is aim at having an insight on the modern application of transition metal complexes in the production of drugs.

Copper Complexes as Anticancer Agents

The variety of metal ion functions in biology has stimulated the development of new metallodrugs other than Pt drugs with the aim to obtain compounds acting via alternative mechanisms of action. Among non-Pt compounds, copper complexes are potentially attractive as anticancer agents. Actually, since many years a lot of researches have actively investigated copper compounds based on the assumption proposal that endogenous metals may be less toxic12.

It has been established that the properties of copper-coordinated compounds are largely determined by the nature of ligands and donor atoms bound to the metal ion. In this review, the most remarkable achievements in the design and development of copper(I, II) complexes as antitumor agents are discussed. Special emphasis has been focused on the identification of structure-activity relationships for the different classes of copper(I,II) complexes. This work was motivated by the observation that no comprehensive surveys of copper complexes as anticancer agents were available in the literature. Moreover, up to now, despite the enormous efforts in synthesizing different classes of copper complexes, very few data concerning the molecular basis of the mechanisms underlying their antitumor activity are available. This overview, collecting the most significant strategies adopted in the last ten years to design promising anticancer copper(I,II) Zinc(II), Nickel(II) and Cobalt(II) compounds, would be a help to the researchers working in this field.

Synthesis, Characterization, Spectroscopy and Anticancer biological activity

A. Synthesis, Characterization and Anticancer Activity of L-Alanine Schiff Base Complexes of Copper(II), Zinc(II),

Nickel(II) and Cobalt(II)

A new series of copper(II), zinc(II), nickel(II) and cobalt(II) complexes with the Schiff base derived from 4-hydroxysalicylaldehyde and L-alanine has been synthesized 9. These compounds have been characterized by elemental analyses, thermoanalyses, conductivity measurements, infrared and electronic spectra. The Schiff base ligand and its zinc(II) complex have been further identified by ^{1}H NMR. The results suggest that the Schiff base acts as a tridentate ligand and the metal ions in the complexes are bonded to the ligand through the phenolic oxygen, imino nitrogen and carboxylate oxygen. All complexes are non-electrolytes. The complexes, except for the cobalt(II) complex, have been found to possess anticancer activity against Ehrlich ascites carcinoma with the copper(II) complex having the highest anticancer activity by the primary screening tests.

B. Synthesis and characterization of cobalt and nickel chelates of 5-dimethylaminomethyl-2-thiouracil and their evaluation as antimicrobial and anticancer agents

A new antimetabolite of adenine, viz. 5-dimethylaminomethyl-2-thiouracil, was synthesized using the Mannich reaction. Owing to the biological importance of metalloelements in many biological processes, especially metabolic processes, cobalt(II) and nickel(II) complexes were also synthesized and examined for their antimicrobial and anticancer activities.13 These new compounds were characterized structurally by various techniques ranging from micro-elemental analyses to spectral analyses. Cobalt(II) complexes were found to be four coordinate, among which the bromo, iodo, and nitrato complexes were polymeric. The nickel(II) isothiocyanato complex exhibited four-coordinate geometry and the remaining nickel(II) complexes were six coordinate. Thermodynamic and kinetic parameters evaluated based on TG/DSC suggested that the initial stage of thermal decomposition follows a diffusion-controlled mechanism and the final stage a chemically controlled mechanism. Antibacterial, antifungal, and antitumor studies undertaken for the above compounds indicated structure–activity relationships. These metalloderivatives were more active than the parent compound. The order of activity was influenced by the chelate geometry and thermal stability. Activity increased with a decrease in coordination number and increase in thermal lability.

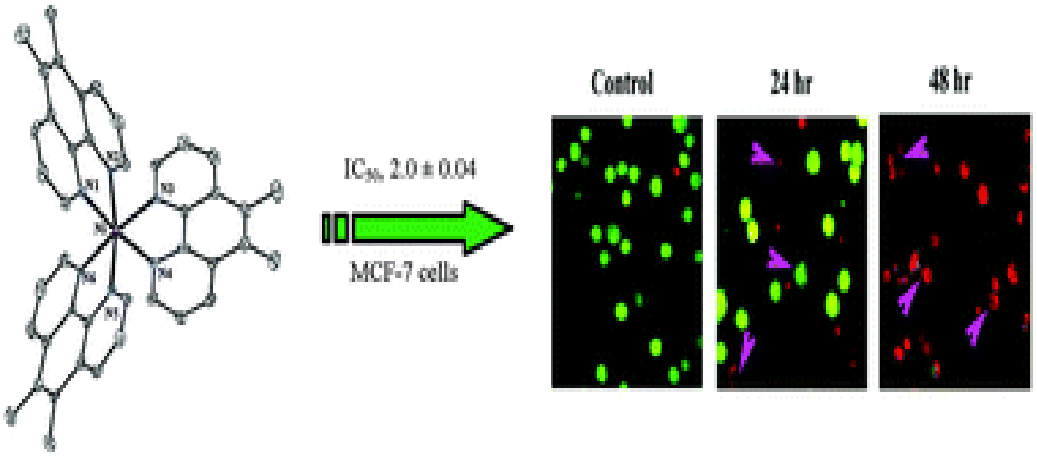
C. Spectroscopic and electrochemical properties of nickel(II), iron(III) and cobalt(II) complexes with benzilbisthiosemicarbazone

Reactions of benzilbisthiosemicarbazone (LH_6) with nickel, cobalt and iron chloride and nitrate give different complexes depending on the salts used and the working conditions. Reactions from nickel chloride give three complexes, on modified pH. nickel(II) benzilbisthiosemicarbazone is obtained in ethanol under reflux, and in methanol, independently of temperature and also with basic medium. iron(III) benzilbisthiosemicarbazone is formed by working in ethanol at room temperature. The ligand acts as a dianion in both complexes. In the presence of hydrochloric acid, the new isolated obalt(II)benzilbisthiosemicarbazone

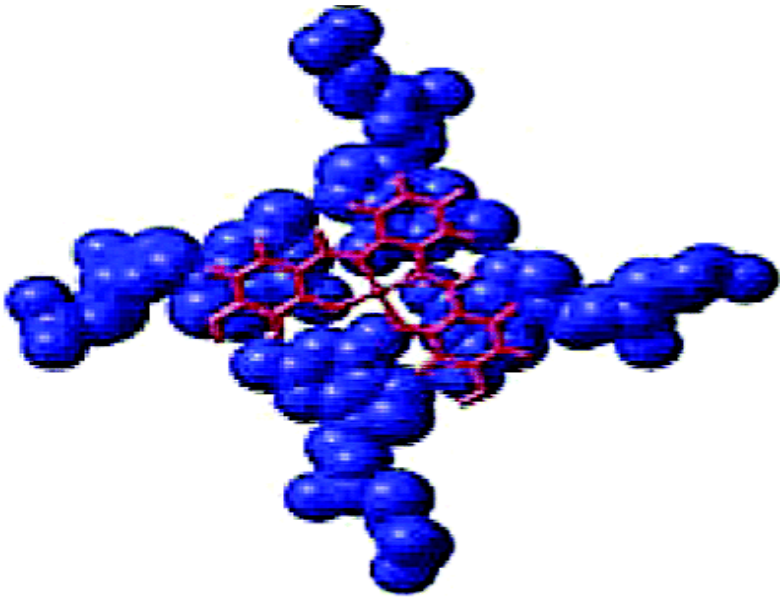
is presents in the neutral form of the ligand. Reaction from nitrate yields only complex 1. Reactions with iron chloride give two new complexes with different formulae and grade of deprotonation in the ligand. For complex 4, obtained at room temperature, LH_6 acts as an anion with a ligand–iron ratio of 2:1 and in its neutral form with a 1:1 ratio in complex 5, working under reflux. Reactions with iron nitrate yield complex 6, with the ligand in an intermediate situation, as anion but a nitrate remains. Complexes 7 and 8, with a 1:1 cobalt–ligand molar ratio are isolated from reactions with cobalt nitrate; both contain nitrate and ethanol or water to complete the co-ordination sphere. Attempts to get a macrocyclic thiosemicarbazone from reaction of benzil and LH_6 in the presence of nickel or iron salt gave the complexes obtained, in absence of the dicarbonyl molecule. Electrochemical behaviour of complexes studied by cyclic voltammetry show metal-centred reduction processes for all of them. The reduction/oxidation potential values depend on the structures of complexes. Nickel complexes exhibit waves corresponding to Ni(III)–Ni(II) process. Electrochemical response of iron complexes depends on the presence of chloride ions.10.

D. Nickel (II) complexes of naphthaquinone thiosemicarbazone and semicarbazone:

Ni(II) complexes of *ortho*-naphthaquinone thiosemicarbazone and semicarbazone were synthesized and spectroscopically characterized. The X-ray crystal structure of both the complexes describe a distorted octahedral coordination with two tridentate mono-deprotonated ligands. In vitro anticancer studies on MCF-7 human breast cancer cells reveal that the semicarbazone derivative along with its nickel complex is more active in the inhibition of cell proliferation than the thiosemicarbazone analogue11.



$[Ni(5,6\text{-dmp})_3]^{2+}$ **(5)** MCF-7 Cells treated with **5**



E. Stabilization of G-Quadruplex DNA and Inhibition of Telomerase Activity by Square-Planar Nickel(II) Complexes

Two new alkylamine-substituted nickel(II)−salphen complexes have been prepared and their interactions with DNA investigated. FRET studies have shown that these complexes have a remarkable ability to stabilize G-quadruplex DNA. Furthermore, TRAP/Taq assays have shown that these complexes inhibit telomerase at low micromolar concentrations.

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